Sedation and Analgesia in the Mechanically Ventilated Patient

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Sedation and analgesia are important components of care for the mechanically ventilated patient in the intensive care unit (ICU). An understanding of commonly used medications is essential to formulate a sedation plan for individual patients. The specific physiological changes that a critically ill patient undergoes can have direct effects on the pharmacology of drugs, potentially leading to interpatient differences in response. Objective assessments of pain, sedation, and agitation have been validated for use in the ICU for assessment and titration of medications. An evidence-based strategy for administering these drugs can lead to improvements in short- and long-term outcomes for patients. In this article, we review advances in the field of ICU sedation to provide an up-to-date perspective on management of the mechanically ventilated ICU patient.

Keywords: conscious sedation; analgesia; delirium; respiratory insufficiency; benzodiazepines

Sedation and analgesia are essential components of care for many mechanically ventilated patients in the intensive care unit (ICU). To choose an optimal strategy of medication use, it is necessary to understand the body of literature that forms the groundwork for evidence-based recommendations (1). Furthermore, the continued scholarly discovery that occurs between the formation of consensus guidelines is important to consider as we await the publication of revised clinical practice guidelines in the near future. This thorough knowledge base is important to formulate a thoughtful management plan that ensures patient comfort while maximizing short- and long-term outcomes.

ANALGESIA

On the topic of sedation in the ICU, it is vital to remember that the management of mechanically ventilated patients under the rubric of "sedation" must first acknowledge the need for adequate pain control. Pain is a symptom frequently experienced by critically ill patients (2, 3). Pain can be experienced as a consequence of intubation and mechanical ventilation itself, or it can be a consequence of other routine clinical care such as moving a patient in bed or adjusting tubes and lines (4). Pain can be substantial and initiate elements of the stress response (5). Accordingly, pain should be addressed to ensure patient comfort and potentially reduce accompanying adverse events (6). It is possible that patients with adequate pain control may require few or no sedatives, as noted by a Danish study discussed in more detail below (7). Although the importance of attention to pain is undeniable (8), it is equally important to recognize that not all mechanically ventilated patients actually experience pain. For example, Puntillo and colleagues described the experiences of 171 ICU patients at high risk of dying. Only 40% of these patients reported pain when interviewed for a period of up to 2 weeks after their ICU experiences (2). This study is important because it confirms that although universal consideration of the possibility of pain is needed, a strategy of universal analgesic administration is unnecessary (9). The optimal way to address analgesia in mechanically ventilated patients in the ICU is to communicate directly with the patient.

Although the need for direct patient communication is self-evident, it may be difficult for a mechanically ventilated patient to communicate symptoms of pain. Several tools are available to assess pain objectively. The Numeric Rating Scale has been validated in critically ill patients, even when delirious, as long as they can communicate by speaking or pointing (10, 11). This scale uses a 0-to-10 scale, anchored by the descriptors "no pain" and "pain as bad as it could be" (12). For this to be an accurate assessment, however, the administrator of the Numeric Rating Scale must be sure to provide a clearly readable scale with descriptors and be steadfast in making sure the patient understands the question with adequate time to respond. The Behavioral Pain Scale and Critical Care Pain Observation Tool, both of which use clinician observations of behavioral pain responses, have been validated for use in mechanically ventilated patients by comparing interrater variability and correlation to the self-reported Numeric Rating Scale (13, 14). However, the Behavioral Pain Scale seems to underestimate higher intensity pain when compared with the self-reported Numeric Rating Scale (10). Neither of these tools has been validated in deeply sedated patients or in assessing the response to pain medications. The Nonverbal Pain Scale incorporates both behavioral and physiological components and can be used in patients who are unable to communicate (15) (Table 1). This tool is used widely but was developed through an observational study validating interrater reliability. A follow-up study of a revised Nonverbal Pain Scale showed that the score does correlate to noxious interventions, although raters were not blinded as to whether the evaluation time was before, during, or after the noxious intervention (16). Although each of these pain assessment tools has limitations, they can be used to help guide administration of analgesics.

A basic understanding of drug pharmacology should guide the choice of which analgesic or sedative to use. Factors specific to the individual characteristics of critically ill patients must be considered. Patients in shock may have decreased hepatic and/or renal blood flow, leading to changes in metabolism and clearance of medications (17). The use of continuous infusions also alters the pharmacokinetics of drugs, which historically have been studied for single-dose administrations (17). Other patient-specific factors such as obesity, which affects the volume of distribution,

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TABLE 1. NONVERBAL PAIN SCALE

	Category		
	0	1	2
Face	No particular expression or smile	Occasional grimace, tearing, frowning, wrinkled forehead	Frequent grimace, tearing, frowning, wrinkled forehead
Activity (movement)	Lying quietly, normal position	Seeking attention through movement or slow, cautious movement	Restless, excessive activity and/or withdrawal reflexes
Guarding	Lying quietly, no positioning of hands over areas of body	Splinting areas of the body, tense	Rigid, stiff
Physiological I (vital signs)	Stable vital signs (no change in past 4 h)	Change over past 4 h in any of the following: SBP > 20 mm Hg, HR > 20 beats/min, RR > 10 breaths/min	Change over the past 4 h in any of the following: SBP > 30 mm Hg, HR > 25 beats/min, RR > 20 breaths/min
Physiological II	Warm, dry skin	Dilated pupils, perspiring, flushing	Diaphoretic, pallor

Definition of abbreviations: HR = heart rate; RR = respiratory rate; SBP = systolic blood pressure.
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and genetic variations, which affect drug response and metabolism, may change how an individual patient responds to a specific medication (18). Therapeutic hypothermia, which is being used increasingly in ICUs, decreases the volume of distribution of drugs, and this leads to changes in plasma concentrations (19). Of critical importance is the understanding of a pharmacological principle referred to as the "context-sensitive half-time" (20, 21) (Figure 1). For all sedative and analgesic agents used in the ICU, plasma drug concentration varies in both magnitude and direction over time; it is dependent on the drug concentration gradients present between various "compartments" (i.e., the bloodstream, the fat tissue, the central nervous system receptors). The context-sensitive half-time describes the time required for the plasma drug concentration to decline by 50% after terminating an infusion. It is dependent on both distribution and metabolism of a given drug. In general, context-sensitive half-time increases with duration of infusion. Some drugs are more prone to this (e.g., benzodiazepines, morphine, fentanyl) (22) than others (e.g., propofol, remifentanil), but any drug can be susceptible to this phenomenon, particularly with long-term infusions (23).

The most commonly used analgesics are in the opioid family. The primary mechanism of action is to stimulate the μ_1 opioid receptor, which inhibits the central nervous system pain response. Other opiate receptors mediate the respiratory depression and sedative effects (24). Opiates shift the CO_2 response curve to the right. The breathing pattern typically seen is a reduction in respiratory rate with preservation of tidal volume (sometimes referred to as "slow and deep"). This is in distinction to the respiratory depression pattern seen with benzodiazepines (see below). In general, opiates are hepatically metabolized and renally cleared. Morphine is broken down into active metabolites that can accumulate in renal failure. As such, there seems little reason to use this medication in the ICU except in those with normal renal function. Hydromorphone is 5 to 10 times more potent than morphine and does not have active metabolites, but the parent drug can accumulate in renal failure, leading to increasing plasma concentrations. Because it is lipophilic, fentanyl has a rapid onset of action; however, its lipophilic pharmacokinetics also leads to deposition into adipose tissue. Patients receiving infusions without interruption may suffer from prolonged effects after discontinuation (25); however, fentanyl does not have any renally excreted metabolites. Remifentanil is a newer opiate that has a short onset of action and is metabolized into inactive metabolites by nonspecific enzymes in the blood, so it is not affected by hepatic or renal failure (26). Although there are few randomized controlled trials directly comparing opiate choices in the ICU, remifentanil seems to be a promising drug with the potential to decrease the prolonged effects of analgesia and potentially reduce the amount of sedative required when compared with morphine or fentanyl (27–31) (Table 2). However, all opioids including remifentanil have the potential to induce tolerance over time, resulting in the need for escalating doses to achieve the same analgesic effect (32). Furthermore, hyperalgesia, or a paradoxical increased sensitivity to pain, can occur particularly with short-acting opioids such as remifentanil (33, 34). A large Chinese cohort study of surgical patients showed that remifentanil-induced hyperalgesia is more likely to occur in patients younger than 16 years old, with doses greater than 30 μg/kg, and in procedures longer than 2 hours (35). This effect is thought to be mediated in part via *N*-methyl-D-aspartate (NMDA) receptors, and the coadministration of ketamine, an NMDA antagonist, may modulate the hyperalgesia response (36). In addition, because remifentanil is eliminated from the body so rapidly, in some cases it may lead to a circumstance in which patients are left with no analgesia after discontinuing the

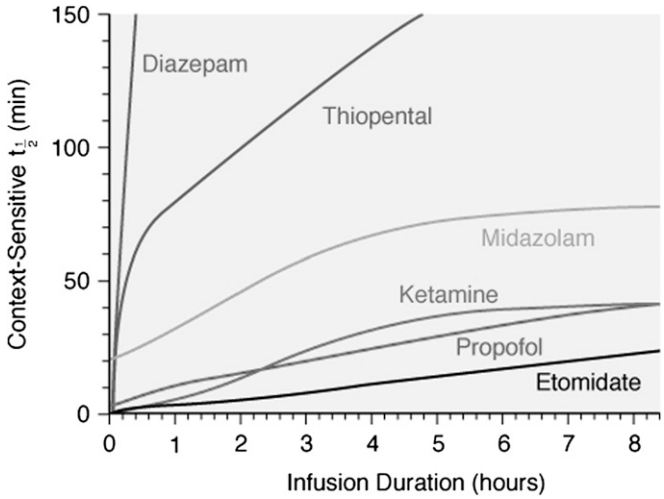

Figure 1. Context-sensitive half-time. As sedative drugs are administered, the context of infusion (i.e., dose, duration of infusion, distribution of drug, metabolic breakdown) is important to consider because the interactions of these variables will determine the drug's half-time. Although a single-dose administration of a drug may have a short half-time, the same drug may have a long half-time when administered as an infusion. Further, each drug will have its own context-sensitive half-time profile. For example, whereas propofol has a modest, but real, increase in half-life with prolonged infusions, midazolam and diazepam increase their half-lives quickly with even short durations of infusion. Reprinted by permission from Reference 165 (adapted by permission from Reference 166).

TABLE 2. SUMMARY OF RANDOMIZED CONTROLLED TRIALS COMPARING ANALGESIC AND SEDATIVE MEDICATIONS

Authors (Ref.)	Patient Population	Medications Compared	Significant Findings
Carrer *et al.* (151)	100 postsurgical pts on MV	Remifentanil + morphine vs. morphine alone	Remifentanil + morphine more effective
Dahaba *et al.* (31)	40 pts on MV	Remifentanil vs. morphine	Remifentanil more effective sedation, more rapid wake-up and extubation
Muellejans *et al.* (152)	152 cardiac, general postsurgical, or medical pts on MV	Remifentanil vs. fentanyl	Remifentanil requires less propofol but greater pain afterward; equally effective sedation
Breen *et al.* (29)	105 pts on MV (UK)	Remifentanil + midazolam prn vs. midazolam + morphine or fentanyl	Remifentanil + midazolam prn (analgesia-based sedation) with fewer days on MV
Muellejans *et al.* (27)	80 cardiac surgery pts on MV	Remifentanil + propofol vs. fentanyl + midazolam	Remifentanil + propofol: Fewer days on MV, fewer days in ICU, equal cost
Rozendaal *et al.* (28)	205 medical or postsurgical ICU pts on MV	Remifentanil + propofol prn vs. usual care (propofol, midazolam, or lorazepam combined with fentanyl or morphine)	Remifentanil + propofol prn: More effective sedation, fewer days on MV, fewer days in ICU
Pohlman *et al.* (153)	20 medical pts on MV	Lorazepam vs. midazolam	Lorazepam trends to more rapid wake-up (NS)
Swart *et al.* (54)	64 pts on MV > 3 d	Lorazepam vs. midazolam	Lorazepam more effective sedation and more cost-effective
Saito *et al.* (65)	35 postsurgical pts on MV (Japan)	Midazolam alone vs. midazolam followed by propofol 24 h before expected extubation	Midazolam–propofol more rapid wake-up, less agitation; equally effective sedation
Grounds *et al.* (154)	60 post–cardiac surgery pts on MV (UK)	Propofol vs. midazolam	Propofol more rapid wake-up, fewer days on MV, more effective sedation
Aitkenhead *et al.* (67)	101 pts on MV up to 24 h	Propofol vs. midazolam	Propofol more rapid wake-up, fewer days on MV
Ronan *et al.* (155)	60 postsurgical pts on MV	Propofol vs. midazolam	Propofol more rapid wake-up, more effective sedation
Kress *et al.* (38)	73 pts on MV	Propofol vs. midazolam	Propofol more rapid wake-up; equally effective sedation
Chamorro *et al.* (66)	98 pts on MV > 48 h	Propofol vs. midazolam	Propofol more rapid wake-up, more effective sedation
Barrientos-Vega *et al.* (68)	108 med–surg pts on MV > 24 h (Spain)	Propofol vs. midazolam	Propofol fewer days on MV, more cost-effective, equally effective sedation
Weinbroum *et al.* (156)	67 pts on MV (Israel)	Propofol vs. midazolam	Midazolam more effective sedation, more cost-effective
Hall *et al.* (63)	59 pts on MV (Canada)	Propofol vs. midazolam	Propofol: Fewer days on MV
Huey-Ling *et al.* (64)	60 pts undergoing elective CABG	Propofol vs. midazolam	Comparable sedation efficacy, hemodynamic stability, and patient satisfaction
Carson *et al.* (69)	132 pts on MV > 48 h requiring significant sedation	Propofol vs. lorazepam bolus	Propofol: Fewer days on MV
Candiotti *et al.* (83)	60 surgical pts on MV > 12 h	Fospropofol bolus/infusion vs. fospropofol infusion vs. propofol infusion	Fospropofol (either method) safe and effective for short-term ICU use
Venn *et al.* (93)	119 postoperative pts on MV (UK)	Dexmedetomidine vs. placebo	Dexmedetomidine requires less midazolam and morphine
Triltsch *et al.* (92)	30 postsurgical patients > 6 h MV	Dexmedetomidine vs. placebo	Dexmedetomidine requires less propofol and morphine, fewer days on MV
Martin *et al.* (89)	401 postsurgical pts on MV	Dexmedetomidine vs. placebo	Dexmedetomidine requires less propofol and morphine
Venn *et al.* (91)	20 abdominal surgery pts on MV	Dexmedetomidine vs. propofol	Dexmedetomidine requires less alfentanil, fewer days on MV, equally effective sedation
Herr *et al.* (90)	95 CABG pts on MV at 25 centers	Dexmedetomidine vs. propofol	Dexmedetomidine requires less morphine, equally effective sedation
Pandharipande *et al.* (85)	106 med–surg pts on MV	Dexmedetomidine vs. lorazepam	Dexmedetomidine: Fewer days of delirium and coma
Pandharipande *et al.* (95)	63 med–surg pts on MV with sepsis	Dexmedetomidine vs. lorazepam	Dexmedetomidine: Fewer days of delirium and coma, fewer days on MV, lower mortality
Riker *et al.* (86)	375 med–surg pts on MV > 24 h	Dexmedetomidine vs. midazolam	Dexmedetomidine: Fewer days of delirium, fewer days on MV
Dasta *et al.* (94)	366 pts on MV > 24 h	Dexmedetomidine vs. midazolam	Dexmedetomidine: Lower costs of MV and ICU
Shehabi *et al.* (157)	306 postop cardiac pts on MV	Dexmedetomidine vs. morphine	Dexmedetomidine: Fewer days of delirium, fewer days on MV
Kong *et al.* (158)	60 pts on MV > 12 h (study only up to 24 h)	Isoflurane vs. midazolam	Isoflurane: More rapid wake-up, more effective sedation
Spencer *et al.* (159)	60 pts on MV > 24 h	Isoflurane vs. midazolam	Isoflurane: More rapid wake-up, fewer days on MV
Sackey *et al.* (97)	40 pts on MV > 12 h (Sweden)	Isoflurane vs. midazolam	Isoflurane: More rapid wake-up, equally effective sedation
Sackey *et al.* (160)	40 pts on MV (Sweden)	Isoflurane vs. midazolam	Isoflurane: Fewer delusions and hallucinations
Meiser *et al.* (161)	60 postsurgical pts on MV	Desflurane vs. propofol	Desflurane: More rapid wake-up
Rohm *et al.* (162)	125 pts with major surgery on MV up to 24 h	Sevoflurane vs. propofol	Comparable wake-up
Mesnil *et al.* (100)	60 pts on MV > 24 h up to 72 h (France)	Sevoflurane vs. propofol vs. midazolam	Sevoflurane: More rapid wake-up and extubation, fewer opiate needs

Definition of abbreviations: CABG = coronary artery bypass graft; ICU = intensive care unit; med–surg = medical–surgical; MV = mechanical ventilation; NS = not significant; prn = as needed; pts = patients.

infusion. If remifentanil is used, care must be taken to anticipate these potential problems.

SEDATION

After the absence of pain is ensured, a patient's sedation needs can be assessed. Pain control alone may allow patients to be comfortable enough to require no sedation (7). Nonpharmacological interventions such as repositioning or verbal reassurance may be helpful to comfort or redirect an agitated patient. However, usually such a nonpharmacological approach alone is inadequate or infeasible. In those instances, pharmacological sedation may be indicated to help relieve discomfort, improve synchrony with mechanical ventilation, and decrease the overall

work of breathing. Most often, one analgesic and/or one sedative medication will be sufficient to achieve these goals. On occasion, a third agent may be added but should be titrated to specific pain and sedation scale goals to prevent adverse outcomes from oversedation and to avoid excessively high doses of the medications, which may result in increased risk for toxicities. Mechanical ventilation provides a reduction in the overall oxygen consumption for patients in critical illness at a time when oxygen delivery may not be optimal (37). Sedation can further help reduce oxygen consumption, as can neuromuscular blockade (38). The use of neuromuscular blocking agents has fallen out of favor because of evidence that they may contribute to prolonged neuromuscular weakness (39, 40); however, a study by Papazian and colleagues demonstrated that neuromuscular blockade may be useful in a select population of patients with early severe acute respiratory distress syndrome when used for a limited timeframe of 48 hours (41). Expert guidelines suggest that neuromuscular blocking agents should be titrated to train-of-four twitch monitoring (42), although results of clinical trials are conflicting when train-of-four monitoring is compared with "clinical judgment" alone (43). Cisatracurium is the preferred neuromuscular blocking agent, because it undergoes spontaneous metabolism by Hofmann degradation. In the rare circumstances in which neuromuscular blocking agents are administered in the ICU, there seems little reason to justify the use of any drug other than cisatracurium. It should be noted that neuromuscular blocking agents do not have amnestic properties, and sedation to the point of amnesia is required if these drugs are used to avoid an awake but paralyzed patient. The use of tools that measure the level of consciousness by algorithmic analysis of a patient's electroencephalogram, such as the Bispectral Index, may be useful when integrated with other tools of sedation monitoring to ensure amnesia in the pharmacologically paralyzed patient (44, 45). There is some evidence from surgical patients that the Bispectral Index correlates well with the depth of sedation and amnesia from propofol or midazolam (46, 47), although the use of this index intraoperatively did not reduce patient awareness compared with the standard technique of end-tidal anesthetic agent concentration that is commonly used by anesthesiologists (48). In addition, deep sedation, as measured by Bispectral Index, has been correlated to a higher long-term mortality in surgical patients (49, 50). Further randomized, controlled studies in the ICU population are necessary before the Bispectral Index can be recommended as the standard of care.

Sedative Medications

Benzodiazepines act through the γ-aminobutyric acid (GABA) receptor. This is a neuroinhibitory receptor that causes neurons to be less excitable when benzodiazepines bind to it. These drugs have anxiolytic, sedative, and hypnotic effects at increasing doses (17). The two most commonly used drugs for ICU sedation in this class are midazolam and lorazepam. Both of these drugs are lipophilic, although midazolam is more so in plasma. This allows it to quickly cross the blood–brain barrier, resulting in a more rapid onset of action (≤1 min) than lorazepam. Lipophilicity also causes both midazolam and lorazepam to accumulate in adipose tissues, where they are not readily metabolized (51). The usual metabolism is via the CYP450 enzyme system in the liver; therefore, liver dysfunction significantly increases the duration of action, particularly with midazolam. In addition, midazolam is broken down into active metabolites that can accumulate in the setting of renal failure; because of this, there seems little reason to use midazolam unless patients have normal renal function (52). These pharmacological properties can make the effects of benzodiazepines linger and cloud a patient's neurological assessment, many times for days if continuous infusions are administered (53). Because lorazepam is less lipophilic, it has a slower onset of action than midazolam. Its metabolites are not active, so it is the preferred benzodiazepine in patients with renal failure (17). In a study that directly compared lorazepam with midazolam, lorazepam resulted in a higher rate of adequate sedation and was more cost-effective than midazolam (54) (Table 2).

A potential adverse effect of benzodiazepines is respiratory depression. These drugs shift the CO_2 response curve to the right. Unlike the opiates, benzodiazepines tend to reduce both respiratory rate and tidal volume, so the "slow and deep" breathing pattern of opiates is less commonly seen with these drugs. These drugs have antiepileptic properties that make them useful for seizures, and they are valuable for use in alcohol and chronic benzodiazepine withdrawal (55). Rarely, there may also be a paradoxical reaction to the drug, resulting in agitation. This unusual response is seen more frequently in elderly patients. There is a high incidence of delirium with benzodiazepines used in ICU patients (56). Of note, patients who have been receiving prolonged infusions of benzodiazepines at high doses in the acute setting are at risk of withdrawal on discontinuation (57). Rarely, propylene glycol, the solvent in which lorazepam is delivered, can cause toxicity. This causes a constellation of symptoms, including a hyperosmolar metabolic acidosis, lactic acidosis, hypotension, and arrhythmias (58). A small observational study found that approximately 20% of patients receiving lorazepam can exhibit signs of propylene glycol toxicity (58). This syndrome seems to be most strongly correlated to higher infusion rates and higher 24-hour cumulative doses (59). Although benzodiazepines have traditionally been used as first-line agents, randomized controlled trials comparing them with newer agents such as propofol or dexmedetomidine clearly show that benzodiazepines lead to worse outcomes, including delirium, oversedation, delayed extubation, and longer time to discharge.

Propofol is another commonly used ICU sedative. The mechanism of action is not well understood, but evidence supports the theory that it acts through modulation of neurotransmitter release, including GABA, and has direct effects on the brain (60, 61). This GABAergic agent is a lipophilic drug that quickly crosses the blood–brain barrier, with an onset of action on the order of seconds to minutes (62). There is also an extremely rapid redistribution of propofol to peripheral tissues, again on the order of minutes, coupled with a large volume of distribution. These pharmacokinetic properties make propofol ideal for early recovery of consciousness after discontinuation of continuous infusions, even when administered for prolonged periods. In a Canadian study, mechanically ventilated ICU patients receiving propofol were extubated more quickly than those receiving midazolam (63). Multiple studies comparing propofol with benzodiazepines consistently support the preferential use of propofol because of the shorter time to mental status recovery, liberation from the ventilator, and cost-effectiveness (38, 63–69) (Table 2). Case series have described propofol for use as an antiepileptic for refractory seizures, and it may have neuroprotective effects in cases of brain ischemia (62, 70). Hypotension is a common occurrence with propofol as a result of decreases in venous and arterial tone and decreased cardiac output, although this is usually of little hemodynamic consequence in volume-resuscitated patients (71). Propofol is formulated in a lipid emulsion, and thus triglycerides should be monitored every 3–7 days while the patient receives continuous infusion, and the 1.1 kcal/ml must be accounted for when formulating a nutrition plan (72). The propofol infusion syndrome is an adverse reaction characterized by bradycardia and cardiac

failure potentially resulting in asystole in the setting of metabolic acidosis, rhabdomyolysis, and hyperkalemia. This condition was originally described in children (73, 74) and led to warnings against propofol in pediatric intensive care (75). This typically occurs at high propofol doses for prolonged infusions. Because many of the data are based on case reports and retrospective reviews, there is considerable debate regarding dosing recommendations; however, most recommend maintaining less than 4 to 5 mg/kg/hour (76–78). The clinician should have a high index of suspicion to recognize this complication, and it may be prudent to monitor pH, lactate, and creatine kinase if high doses or long infusion periods are necessary (78, 79). Fortunately, in adults the occurrence rate of propofol infusion syndrome is rare.

Fospropofol, a prodrug of propofol, is emerging as a potential alternative agent for sedation in the ICU. It is metabolized *in vivo* to the active drug propofol, but the parent drug is water-soluble, with a much smaller volume of distribution than propofol (80). The potential implications of this characteristic include a lower propensity for accumulating in adipose stores during prolonged infusions, although until more recently it had been studied only in phase III clinical trials for colonoscopy, bronchoscopy, or minor surgical procedures (80–82). A pilot study suggests it may also be safe and effective for short-term use in the ICU (83). Contamination of the drug, which is a problem in the lipid formulation of propofol, is less of a concern with the water-soluble fospropofol. The onset of action is slightly longer than that of propofol because it must first be metabolized to the active form, but it is still on the order of minutes. It is safe to use in moderate renal insufficiency but has not been studied yet in liver failure. Further study is necessary to determine whether it is safe and effective to use for prolonged infusions in the ICU.

Dexmedetomidine is an α_2 agonist that acts centrally to inhibit norepinephrine release. It has both sedative and analgesic effects, making it a potentially ideal drug for ICU sedation. It does not have the respiratory depressant effects that are present with most other sedative drugs (84). It allows for a more awake, interactive patient and is associated with less delirium than benzodiazepines (85–87). This drug originally obtained approval by the U.S. Food and Drug Administration for use only in short-term sedation, such as in perioperative settings, because of a lack of data supporting its use in longer term settings (88). Subsequently, Riker and colleagues have studied the drug for longer term infusions and found that dexmedetomidine compared with midazolam in the ICU resulted in less ICU delirium and fewer days of mechanical ventilation, despite equal achievement of sedation level targets (86). Other studies also indicate that patients receiving dexmedetomidine require fewer opiates and other sedative agents and that dexmedetomidine results in less time in a coma state, allows for quicker liberation from the ventilator and discharge from the ICU, and results in less delirium (85, 89–95) (Table 2). The primary significant side effects of dexmedetomidine infusion are bradycardia and hypotension, which may be mitigated by avoiding a loading dose and initiating a slow infusion rate (86, 96). In addition, a withdrawal syndrome characterized by agitation, tachycardia, and hypotension can result on discontinuation of a long-term infusion (88).

Inhaled volatile anesthetics, such as isoflurane and sevoflurane, have been used in the operating room for many years but so far have not been used in the ICU on a widespread basis. The impediment to using these drugs in the past has been difficulty with conservation of the volatile gases. This has been simplified with use of the AnaConDa system (Hudson RCI, Upplands Vasby, Sweden), which can be attached to mechanical ventilators to recycle the anesthetic drug (97). Use of an inhaled volatile anesthetic is an attractive and novel approach to ICU sedation. Inhaled anesthetics have a much better pharmacokinetic profile than many intravenous sedatives, resulting in more adequate sedation and a much quicker, more reliable time to awakening, extubation, and ICU discharge in the postoperative setting (98, 99). A trial comparing sevoflurane, using the AnaConDa system, with propofol or midazolam demonstrated safety, efficacy, and shorter times to extubation with fewer opiate requirements in the ICU study (100) (Table 2).

Sedation Strategy

When a clinician chooses to prescribe sedatives, validated sedation scales and protocols should be used to guide titration of these medications. The Ramsay Sedation Scale (RSS) is one of the most widely used sedation tools for evaluating level of consciousness (101). The Sedation–Agitation Scale (SAS) built on the RSS to further stratify the agitation end of consciousness (102). The Adaptation to the Intensive Care Environment (ATICE) Scale is a more comprehensive tool that assesses both the consciousness of the patient and tolerance of the ICU environment (103). The Nursing Instrument for the Communication of Sedation (NICS), which was made with the intent of a more simplified and easily recalled system for clinical use, was validated against prior sedation scales but has yet to be validated for monitoring sedation over time (104). The Richmond Agitation–Sedation Scale (RASS) attempts to capture arousal, cognition, and sustainability of response (Table 3). It has been validated for interrater reliability in the ICU and for titration of sedation over time (105, 106). This scale is the most extensively validated and is, accordingly, one of the most widely used in the management of critically ill patients. Most uncomplicated patients in the ICU should be titrated to an RASS score not less than –2. Rarely, a patient who is extremely ill may be targeted to a deeper sedation level of –3 or –4 if this will facilitate necessary care; however, even in these patients, deep sedation may not always be required. For example, in a randomized controlled study of early mobilization in the ICU, sedation was interrupted completely on a daily basis for early physical and occupational therapy. More than half of all therapy sessions involved patients with acute lung injury, more than one-third of sessions were done with a fraction of inspired oxygen above 60%, and approximately 15% of sessions were done while a vasoactive agent was infusing (107). Use of these sedation scales in a protocolized manner, particularly with input from the bedside nurse, can help guide therapy to a targeted sedation level and improve patient outcomes (108, 109).

There are a variety of sedation strategies that have been studied, including daily interruption of sedation and goal-directed sedation algorithms. Medications can be given in the form of continuous drips, but active drugs and metabolites can accumulate for all the reasons discussed previously, so careful attention is important to maintain a minimal amount of medication that still succeeds in producing adequate analgesia and sedation. Daily interruption of continuous sedation infusions was shown to decrease the number of days of mechanical ventilation and in the ICU (110). It also allowed for a better assessment of neurological status, decreasing the need for diagnostic neurological testing. If a patient required resumption of sedative infusions, they were started again at half the previous dose in this protocol.

In addition to daily interruption of sedatives, other nursing-implemented protocols have demonstrated promising results. Brook and colleagues used a bedside nursing protocol to titrate analgesia and sedation to a specific goal of 3 on the Ramsay Sedation Scale (108). This resulted in shorter duration of mechanical ventilation, ICU stay, and hospital stay when compared with usual care. Patients on the protocol also had a lower incidence of tracheostomy. De Jonghe and colleagues used the

TABLE 3. RICHMOND AGITATION–SEDATION SCALE

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 s) awakening, with eye contact in response to voice
−2	Light sedation	Briefly (less than 10 s) awakens with eye contact in response to voice
−3	Moderate sedation	Any movement (but no eye contact) in response to voice
−4	Deep sedation	No response to voice, but any movement in response to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Procedure

1. Observe patient. Is patient alert and calm (score 0)?
   Does patient have behavior that is consistent with restlessness or agitation (score, +1 to +4 using the criteria listed under Description)?
2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker.
   Repeat once if necessary. Can prompt patient to continue looking at speaker.
   Patient has eye opening and eye contact, which is sustained for more than 10 s (score, –1)
   Patient has eye opening and eye contact, but this is not sustained for 10 s (score, –2)
   Patient has any movement in response to voice, excluding eye contact (score, –3)
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder.
   Patient has any movement to physical stimulation (score, –4)
   Patient has no response to voice or physical stimulation (score, –5)

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ATICE sedation tool to implement a nursing-led algorithm with physician collaboration in decision-making for sedation use. They were able to demonstrate fewer days of mechanical ventilation and in the ICU (109). One study has shown a nursing-implemented sedation protocol to have significantly improved outcomes compared with daily sedative interruption (111), although these findings have not been reproducible and contrast with the numerous studies showing improved outcomes with daily sedative interruption (69, 110, 112). A pilot study from the Canadian Clinical Trials Group compared a nurse-driven sedation protocol paired with daily awakenings versus the sedation protocol alone and demonstrated the feasibility and safety of the study; a multicenter randomized clinical trial is currently underway (113, 114). Interestingly, protocolized sedation management did not yield improved outcomes over usual care when reported in one Australian study. A number of factors may have influenced these findings, including more direct sedation and ventilator management by nursing staff, a lower nurse-to-patient ratio, and possible noncompliance with the study protocol because of the unblinded nature of the study (115). An observational study showed that a novel strategy of patient-controlled sedation in stable, alert patients who can follow commands produced better patient and nurse satisfaction with the level of sedation (116). Strom and colleagues reported the results of a randomized trial comparing a strategy of "no sedation" with daily sedative interruption. Patients in the "no sedation" group received morphine as needed. Patients receiving no sedation had more days without ventilation and a shorter stay in the ICU and hospital. Self-extubations were not different between the groups (7). A multidisciplinary approach to sedation may be the ideal strategy for improved patient outcomes. To accomplish this, education surrounding pain and sedation scales and the use of sedation protocols is necessary for physicians and nurses directly involved with critical care. A working knowledge of the pros and cons of the various sedation strategies (Table 4) is important to formulate a feasible analgesia and sedation algorithm for an individual ICU (Figure 2).

Sedation strategy is important to consider for the potential short-term outcomes benefits of fewer days of mechanical ventilation or in a hospital, but there are also long-term effects related to the sedation strategy used in the ICU. Pairing daily interruptions with spontaneous breathing trials leads to more ventilator-free days than spontaneous breathing trials on their own, and it also leads to decreased mortality at 1 year (112). The alert patient can also more fully participate in rehabilitation, and initiation of physical and occupational therapy during daily awakenings improves recovery of function by the end of the hospital stay (117). Posttraumatic stress disorder (PTSD) after critical illness with respiratory failure is well described and may be associated with increased sedation use (118, 119). Daily sedative interruption has been shown to reduce PTSD in one study (118) and did not show any difference compared with control in another study, although this was a substudy that may not have been adequately powered to detect a difference (120). Treggiari and colleagues found that patients who were targeted to lighter sedation were less likely to experience PTSD or disturbing memories than those who were deeply sedated (121). Sedative and opioid exposure is a risk factor for delirium in the ICU, which may be an indicator of poor prognosis in the critically ill patient (122, 123).

DELIRIUM

Delirium is characterized by an acute onset of disturbance in cognitive abilities with a fluctuating course over time. It is a form of brain dysfunction and a marker of illness in the ICU. Various studies have reported a wide range of incidence, from 11 to 87% (124). Risk factors that may be associated with the development of delirium are multifactorial and include medical conditions such as dementia or hypertension, severity of illness (as indicated by markers such as APACHE scores), social factors such as alcoholism, and medications (in particular, sedatives and opioids) (123, 125). Even when patients are targeted to light sedation, delirium incidence is high and associated with poor outcomes, including increased mortality, ventilator days, and ICU length of stay (126, 127). There is an association between delirium and decreased functional status at hospital discharge (128). Beyond the timeframe of

TABLE 4. SUMMARY OF RANDOMIZED CONTROLLED TRIALS COMPARING SEDATION STRATEGIES

Authors	Patient Population	Methods Compared	Significant Findings
Kress *et al.* (110)	128 med pts on MV	DIS vs. usual care	DIS with fewer days of MV, fewer days in ICU
Anifantaki *et al.* (163)	97 med–surg pts on MV (Greece)	DIS vs. usual care	No difference
Girard *et al.* (112)	336 pts on MV	DIS with daily SBT vs. usual care with daily SBT	Paired DIS + SBT with fewer days of MV, fewer days in ICU and hospital, lower mortality
Yiliaz *et al.* (164)	50 pts on MV	DIS vs. RSS-based protocol	DIS with more rapid wake-up and fewer days of MV
de Wit *et al.* (111)	74 med pts on MV	DIS vs. RSS-based protocol (Brook *et al.*) (108)	Protocol with fewer days of MV, fewer days in ICU and hospital
Brook *et al.* (108)	321 med pts on MV	RSS-based protocol vs. usual care	Protocol with fewer days of MV, fewer days in ICU and hospital, less need for tracheostomy
Bucknall *et al.* (115)	312 pts on MV	RSS-based protocol (Brook *et al.*) (108) vs. usual care	No difference
Mehta *et al.* (113)	65 pts on MV > 48 h	SAS-based protocol vs. SAS-based protocol + DIS	Protocol and protocol + DIS both feasible and safe
De Jonghe *et al.* (109)	102 pts on MV > 24 h and no brain injury	ATICE-based protocol vs. usual care	Protocol with more rapid wake-up and fewer days of MV
Strom *et al.* (7)	140 pts on MV > 24 h	No sedation vs. propofol with DIS	No sedation with fewer days of MV

Definition of abbreviations: ATICE = Adaptation to the Intensive Care Environment; DIS = daily interruption of sedation; ICU = intensive care unit; med = medical; MV = mechanical ventilation; pts = patients; RSS = Ramsay Sedation Scale; SAS = Sedation–Agitation Scale; SBT = spontaneous breathing trial; surg = surgical.

hospitalization, delirium also predicts mortality, decreased quality of life, and poor cognitive outcomes in the long-term setting (127, 129, 130).

One of the difficulties in accurately addressing delirium has been underrecognition of the condition (131). The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) has been a well-validated tool for delirium assessment and may be helpful in tailoring therapy (132, 133). However, van Eijk and colleagues demonstrated that although the CAM-ICU remains highly specific, the sensitivity decreases to almost half when used in a real-world setting (134). Whether this is an imperfection of the tool itself or of the technique of administering it is impossible to determine, and further study is warranted in this area to ensure it remains a good screening method. The Intensive Care Delirium Screening Checklist (ICDSC) is an alternative, slightly more in-depth tool to evaluate for delirium that correlated well when tested against the CAM-ICU in one set of patients (135, 136). In another set of patients the ICDSC was more sensitive in detecting ICU delirium, although the CAM-ICU was equally sensitive and more specific in detecting clinically significant delirium associated with poor patient outcomes (137). Delirium in the ICU has emerged as an important predictor of morbidity and mortality in these patients, and further study is needed to determine strategies for prevention and management.

At present, there is modest evidence to support the effect of nonpharmacological interventions on ICU delirium. Many of the predisposing factors that affect ICU patients also affect other hospitalized patients, and interventions targeted toward these risk factors have been effective to decrease the incidence of delirium in these other populations (138). Employment of simple techniques such as reorientation, enhancement of the sleep environment, and minimization of medications associated with delirium can help decrease the incidence. Early mobilization has been shown to decrease delirium in the ICU. A protocol of daily combined awakening and breathing in conjunction with early mobilization may not only decrease the incidence of delirium, but also improve other important outcomes such as mortality (112, 117). Minimization of sedation and choice of agent may also affect delirium. In particular, dexmedetomidine has

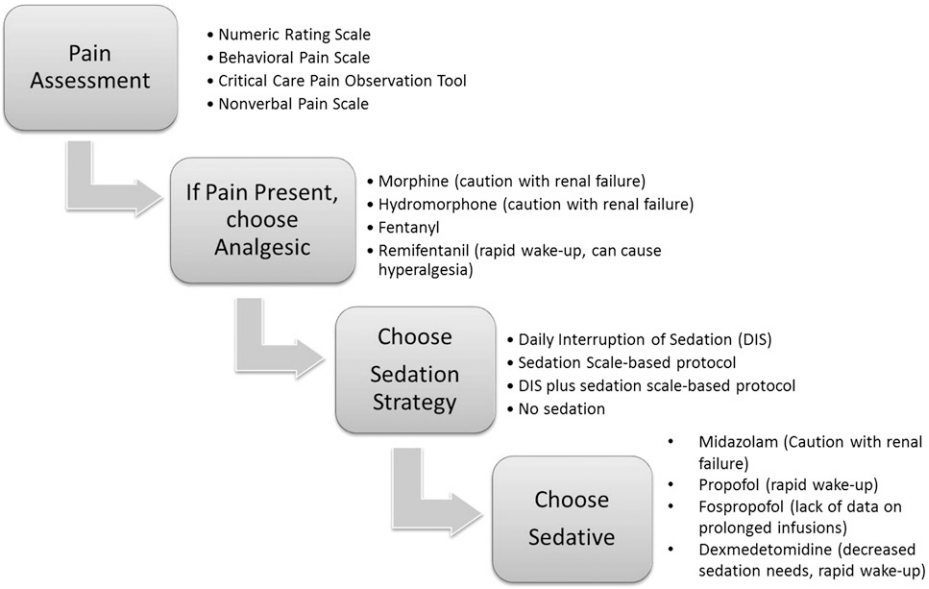

Figure 2. Analgesia and sedation algorithm. A systematic approach to an analgesia and sedation strategy is vital to address patient needs while preserving the ability to assess for improvement in neurological and respiratory status. A specific pain assessment tool should be used to identify pain and titrate analgesic medications. A specific sedation strategy should be chosen, and if a sedative is needed, the choice should be based on a careful weighing of sedative effect, duration of action, and other patient-specific factors such as renal failure. Importantly, the pain and sedative needs should be reassessed frequently to develop an optimal strategy for a particular patient.

been studied with specific interest in its decreased propensity to cause delirium and improved mortality when compared with benzodiazepine-based sedation; this effect may be more pronounced in septic patients (85, 95). The mnemonic "ABCDE" has been proposed as an evidence-based bundle to remind clinicians of important steps of ICU care (*A*wakening and *B*reathing, *C*hoice of sedative and analgesic, *D*elirium monitoring, and *E*arly mobilization) (139). When delirium develops despite these preventive therapies and nonpharmacological interventions, medications directed at delirium treatment are sometimes considered.

Antipsychotics are sometimes employed for symptoms of agitation and delirium in the ICU. Haloperidol is the most commonly used drug, although other atypical antipsychotics are becoming more widespread in use, with a suggestion of efficacy in treating delirium (140, 141). More data are needed to test whether these preliminary studies will translate into improved outcomes regarding ICU delirium. Typical antipsychotics, such as haloperidol, block dopamine receptors in the brain and lead to tranquility. They tend to reduce initiative and interest in the environment as well as manifestations of emotion. Patients are typically drowsy and slow to respond to external stimuli. However, they can usually be aroused, can answer questions, and are able to retain intact cognition. The antidopaminergic action also can result in extrapyramidal side effects such as dystonia, akathisia, and pseudo-parkinsonism. These conditions can usually be reversed with the use of diphenhydramine or benztropine. Neuroleptic malignant syndrome (NMS) is characterized by fever, muscle rigidity, and autonomic dysfunction that a clinician must recognize early to prevent the potential complication of death. Bromocriptine, dantrolene, and benzodiazepines can be used to treat NMS (142). Haloperidol is also associated with prolonged QT interval and torsades de pointes (143, 144). Atypical antipsychotics, such as quetiapine, risperidone, olanzapine, and ziprasidone, block both dopamine and serotonin receptors, with a higher ratio of serotonin blockade to dopamine blockade (145). They may be as effective as haloperidol with fewer extrapyramidal side effects (146). Those atypical antipsychotics with the highest serotonin-to-dopamine blocking ratios are least likely to cause extrapyramidal side effects (145).

There is no convincing evidence for the use of antipsychotics in the treatment of ICU delirium; however, the existing literature in this area is worthy of discussion. Use of haloperidol in a retrospective study was noted to have an association with lower mortality in ventilated patients (147). A small pilot study comparing haloperidol, ziprasidone, and placebo given to delirious patients in a preemptive manner found no difference, although this study may have been underpowered to detect a difference (148). A randomized trial comparing haloperidol with olanzapine showed similar reductions in delirium in both groups; however, extrapyramidal side effects were noted in 6 of 45 haloperidol patients, compared with none in the olanzapine group (141). Combination of a scheduled atypical antipsychotic with haloperidol as needed may be more effective in treating delirium and improving outcomes than haloperidol alone (149).

Agents other than antipsychotics have been investigated as well for treatment of delirium. As noted previously, Riker and colleagues reported a significant reduction in ICU delirium in patients randomized to receive dexmedetomidine compared with midazolam (86). A trial evaluated the cholinesterase inhibitor rivastigmine for the treatment of ICU delirium (150). Patients with delirium were randomized to receive either rivastigmine or placebo. In an interim analysis after randomization of 104 patients—54 of whom received rivastigmine—the trial was stopped because of higher mortality in the rivastigmine group (22 vs. 8%; $P = 0.07$). There was a longer duration of delirium noted in the rivastigmine group as well (5 vs. 3 d; $P = 0.06$). This study is a reminder to us that delirium is a complicated, multifactorial condition that reflects the interaction of a patient's underlying conditions, precipitating factors, and current illness. Ideal management requires screening to improve early recognition and preventive interventions; use of certain pharmacological treatments may be an adjunctive therapy, although there is a need for large, well-done trials before this can be recommended.

CONCLUSIONS

A broad knowledge of analgesia and sedation for mechanical ventilation is important to optimally manage an ICU patient. This includes a basic familiarity with specific agents that are commonly used, in addition to awareness of ICU-specific factors that alter the pharmacology of the drugs. Formal tools for analgesia, sedation, and delirium assessment should be used to help titrate medications to the ideal dose for an individual patient. An evidence-based approach to analgesia and sedation can help improve both short- and long-term outcomes.

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